PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference p26283PC00/HSE	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/NL 02/00720	International filing date *(day/month/year)* 08.11.2002	Priority date *(day/month/year)* 08.11.2002
International Patent Classification (IPC) or both national classification and IPC C12N9/96		
Applicant AVANTIUM INTERNATIONAL B.V.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
03.06.2004	08.02.2005

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/NL 02/00720

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-10 as originally filed

Claims, Numbers

1-16 as originally filed

Drawings, Sheets

1/2-2/2 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	4, 6, 9-16
	No:	Claims	1-3, 5, 7, 8
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-16
Industrial applicability (IA)	Yes:	Claims	1-16
	No:	Claims	

2. Citations and explanations

   see separate sheet

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. **Documents**

1.1 Reference is made to the following documents:

1.2 **D1**: López-Serrano et al., Biotech. Lett., vol. 24, Aug. 2002, pp. 1379-1383
D2: EP1088887
D3: Cao et al., Organic Letters, vol. 2, 2000, pp. 1361-1364
D4: WO0040331

2. **Novelty** (Art. 33(2) PCT)

2.1 The present application does not satisfy the criterion set forth in Article 33(2) PCT because **the subject-matter of claims 1-3, 5, 7 and 8 is not new** in respect of prior art as defined in the regulations (Rule 64(1)-(3) PCT).

2.2 **D1** discloses (pages 1379-1380; Tables 1 and 2) a method for creating Crosslinked Enzyme Aggregates (CLEA) comprising an aggregation step and a crosslinking step. The method is based on a basic recipe ("general procedure"; page 1380, left column, second paragraph) that is then varied to arrive at CLEA:s with different properties. CLEA:s with suitable properties can then be selected. Claims 1-3, 5, 7 and 8 are, therefore, not novel over **D1**.

2.3 **D2** discloses ([0009]-[0011]) a method for creating Crosslinked Enzyme Aggregates (CLEA) comprising an aggregation step and a crosslinking step. **D1** further discloses ([0012]-[0014]; examples) variations that can be performed, in order to arrive a CLEA:s with different properties. Claims 1 and 5 are, thus, not novel over **D2**.

2.4 Claims 4, 6, 9-16 seems to contain subject-matter that is novel over the cited prior art documents.

3. **Inventive step** (Art. 33(3) PCT)

3.1 The present application does not satisfy the criterion set forth in Article 33(3) PCT because **the subject-matter of claims 1-16 does not involve an inventive step** (Rule 65(1)(2) PCT).

3.2 All claims found to be not novel are also considered as not inventive. Even if novelty could be reinstated for these claims, no inventive activity can be accepted for the below reason.

3.3 Claim 1 is concerned with a method for creating a library of CLEA:s, wherein the CLEA is prepared by a method comprising an aggregation step and a crosslinking step. The method is performed according to a basic recipe, that is then varied to obtain the CLEA:s of the library.

3.4 Document **D2** is considered to represent the most relevant state of the art and discloses ([0009]-[0011]) the method of the basic recipe of the present application, and also that variations in this recipe can be performed ([0012]-[0014]; examples).

3.5 The subject-matter of claim 1 differs in that a "library" of CLEA:s is created.

3.6 A library of CLEA:s is, however, nothing else than a number of CLEA:s, each with a somewhat different property. This is not different from what is obtained by varying the method of **D2**, as exemplified in the examples of **D2**. Claim 1 can, thus, neither be seen as being novel, nor as involving and inventive step.

3.7 Furthermore, regardless of, if **D2** describes variations of the basic recipe, such variations can not be regarded as inventive. Such variations are simply what any person skilled in the art would do, and has always done, when faced with the problem to obtain a somewhat different product (CLEA). He would then vary (one or several) of the parameters of the basic recipe used and choose, from the "library" so produced, the product (CLEA) showing the optimal properties. If he does these variation in parallel or after each other, is up to his own liking. Such variations of a basic recipe is also disclosed in **D1** (page 138, left column, second paragraph) and **D3** (page 1362, right column; fig. 2). No inventive activity can, thus, be accepted for claim 1.

3.8 Dependent claims 2-11, do not seem to contain any subject-matter that could not be

arrived at from **D2**, by a person skilled in the art, without applying inventive skill, either directly or by combining with the general technical knowledge of such a person.

3.9 Claim 12 is concerned with a system using the method of claim 1.

3.10 Systems for more or less automatic methods are well-known in the art, e.g. **D4** (page 13, line 5 - page 14, line 28; figures). To combine such a system with the non-inventive method of claim 1 would be obvious for a person skilled in the art wanting to automate the production of CLEA libraries. No inventive activity can, therefor, be accepted for claim 12.

3.11 Dependent claims 12-16, do not seem to contain any subject-matter that could not be arrived at from **D2**, by a person skilled in the art, without applying inventive skill, either directly or by combining with **D4** and/or the general technical knowledge of such a person.

4. Further comments

4.1 In agreement with the requirements of Rule 5.1(a)(ii) PCT documents **D2-D4** should be identified in the description and their relevant subject-matter briefly discussed.

4.2 The statement of page 1, line 10 might not be acceptable in certain regional procedures (e.g the European).